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# TCT@ACC-i2: Invasive and Interventional Cardiology

## SIROLIMUS-FKBP12.6 IMPAIRS ENDOTHELIAL BARRIER FUNCTION THROUGH PKCALPHA ACTIVATION AND DISRUPTION OF THE VE CADHERIN-P120 CATENIN INTERACTION

Oral Contributions
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**Background:** Drug eluting stents (DES) utilizing mTOR inhibitors reduce restenosis but are associated with accelerated neoatherosclerosis. Impaired endothelial barrier function (EBF) is likely contributor to neoatherosclerosis seen in DES.

**Methods:** Human aortic endothelial cells (HAEC) and mouse aortic endothelium (MAE) were examined to determine the effect of sirolimus (SRL), an mTOR inhibitor, on EBF.

**Results:** EBF, measured by transendothelial electrical resistance, was impaired in HAEC with SRL treatment or transfection with siRNA for FKBP12.6. This impairment was reversed when pretreated with ryanodine, a stabilizer of RyR2 Ca2+ release channels. Intracellular Ca2+ increased in HAEC treated with SRL and normalized with ryanodine. HAEC treated with SRL demonstrated increases in PKCalpha phosphorylation, a serine/threonine kinase important in VE cadherin barrier function through its interaction with p120-catenin. Immunostaining of both HAEC and MAE showed disruption of VE cadherin (green) and p120 (red) in cells/aortas treated with SRL (figure). SRL impairment of EBF was abolished by HAEC transfection with PKCalpha siRNA. Mice treated with SRL demonstrated increased MAE permeability measured by Evans blue.

**Conclusion:** SRL binding to FKBP12.6 impairs EBF by increasing intracellular Ca2+ concentration leading to PKCalpha activation and disruption of the VE Cadherin-p120 interaction. Poor EBF may contribute to accelerated neoatherosclerosis seen within DES that utilize mTOR inhibitors.